IS DIABETES AN IATROGENIC DISEASE?

This Viewpoint questions whether both insulin and non-insulin diabetes (T1D and T2D respectively) are iatrogenic diseases, caused mainly by antibiotics. Both T1D and T2D have reached epidemic proportions internationally and increases over the decades mimic that of the consumption of antibiotics. This article will explain the mechanism by which destruction of the beta-cells of the pancreas which produce insulin can occur, and why antibiotics are primarily to blame. It will also describe factors which explain why studies may not find a link.

Diabetes was once thought to be a familial disease, then it was blamed on a virus after which came the hygiene hypothesis and it's now all about the microbiome. However, the variation in incidence of T1D and T2D and tremendous rapid increases internationally since 1965[1], point to environmental factors being causative. Bach and Chatenoud[2] claimed that the increasing frequency can be explained by a decline in infections as we have a better quality of life.

If this better quality of life or differences in the microbiome were to blame, why would countries with similar living standards have different rates? If we look at T1D in children, in 2013[3] the incidence per 100,000 for Singapore with excellent living standards was 2·5, ranking it 67 in the world. In comparison, Sweden which also has excellent living standards and ranks at number 2, second only to Finland, has an incidence of 43·1. The improvement in living standards had probably also levelled out by 1980 but T1D has continued to increase in the UK, USA and Australia as well as other countries. However, the increase in incidence of both T1D and T2D in many countries corresponds to an increase in the consumption of pharmaceuticals, especially antibiotics.

If we look at the chemical structure of drugs, many contain a carbonyl group (C=O) which consists of a carbon atom (C) doubly bonded to an oxygen atom (O). The electrons in the double bond are pulled towards the oxygen due to oxygen's higher affinity for electrons which are negatively charged. This gives the oxygen a negative charge. A nitroso group (N=O) consists of a nitrogen (N) doubly bonded to oxygen, with the oxygen like that in a carbonyl group having a negative charge. The negative charge on the oxygen ion as it is now called, due to its negative charge, enables it to bind to positively charged metal ions such as zinc cations (Zn^{2+}) which are bound to insulin in the beta-cells of the pancreas.

Two diabetogenic chemicals alloxan (fig.1) and streptozotocin an antibiotic (fig.2) have for over sixty years been used to make rodents diabetic to study diabetes. Alloxan has four carbonyl groups and streptozotocin has one carbonyl and one nitroso group. In chemical shorthand the symbol for carbon is omitted in chemical drawings.

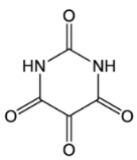

Fig.1 Chemical structure of alloxan discovered to be diabetogenic in 1942.

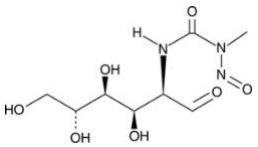

Fig.2 Chemical structure of the antibiotic streptozotocin discovered to be diabetogenic in 1963.

Since streptozotocin is also used in humans to treat certain cancers of the islets of Langerhans because it *destroys* beta-cells of the pancreas which produce insulin, it seems fair to postulate that alloxan could also make humans diabetic, if negatively charged oxygen ions are involved in destruction of beta-cells. In the pancreas insulin is bound to zinc, and it has been shown that antibiotics can bind to metal ions such as $zinc^{2+}$. Support for the claim that drugs can bind to zinc is described below.

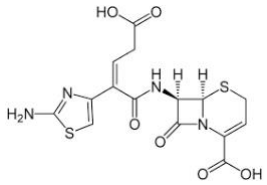

Fig.3 Chemical structure of the antibiotic ceftibuten.

Plasma concentration of ceftibuten (fig. 3) a cephalosporin, was found to have decreased after intraintestinal administration in the presence of zinc[4]. This shows that it can bind positively charged zinc cations. Ceftibuten like alloxan has four negatively charged oxygens.

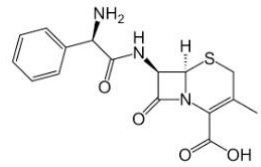

Fig.4 Chemical structure of cephalexin first marketed in 1969.

Ding[5] et al found significant interaction between zinc and cephalexin (fig. 4) another cephalosporin. Healthy volunteers given zinc sulphate together with cephalexin had significantly decreased peak serum concentrations of cephalexin. Administration of zinc three hours *before* cephalexin also decreased the peak serum level, so zinc in food and drink are also likely to bind to cephalexin.

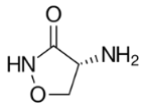

Fig.5 Clycloserine an antibiotic used to treat tuberculosis has one carbonyl group.

Cycloserine (fig.5) was found by Niebergal in 1966[6] to complex with zinc. All five chemicals shown above have negatively charged oxygens as part of a carbonyl (C=O) or nitroso (N=O) group.

Furthermore, zinc supplementation has been reported to prevent alloxan-induced diabetes by Tadros et al[7] and Yang and Cherian[8] and others. Supplementation of zinc by subcutaneous or intraperitoneal injection, drinking water and dietary food have all been shown to be effective in preventing diabetes in rodents[9].

It has also been shown that diabetogenic chemicals that can bind to zinc are able to permeate membranes and complex with zinc in cells. It is thought that they can enter the pancreatic beta-cells which solubilizes the zinc-insulin aggregates and changes the acidity of the cells, causing them to swell and *rupture*[10]. As a result, the beta-cells are no longer able to produce insulin. Maske in 1952[11] showed that histochemical analysis of pancreatic beta-cells exposed to alloxan had lost zinc, which is proof that they burst.

Scientists have shown that animals don't become diabetic if they are fed certain foods that can bind to antibiotics. The sugars mannose and fructose have been shown by Gangagobinda in 1953[12] to protect rodents from diabetes as have trace minerals[7,13,14.] Since these sugars and the trace elements zinc, cobalt, iron, copper and manganese can protect against alloxan-induced diabetes, any study looking for a link between antibiotics and diabetes would need to know what foods were eaten before, with, or after taking an antibiotic. There are many foods which contain these trace elements and infant formula is fortified with iron and some trace minerals, so food is a very important factor that must be taken into consideration.

All of the trace elements iron, zinc, cobalt and manganese can exist as positive ions. Iron can exist as Fe^{2+}, cobalt as Co^{2+}, copper as Cu^{2+}, manganese as Mn^{2+} and zinc as Zn^{2+}. Their positive charge enables them to bind to negatively charged oxygen ions present in penicillins and cephalosporins and other drugs.

Many drugs have one carbonyl group but less than 5% have two or more carbonyl groups.

It's just that antibiotics such as amoxicillin and cephalexin which have three carbonyl groups are amongst the most frequently prescribed drugs in the UK, USA and Australia. So it is more likely that a disease resulting from exposure to antibiotics, rather than other less frequently prescribed drugs will be discovered.

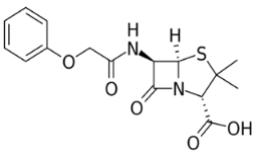

Fig.6 Ampicillin available since 1961 has three carbonyl (C=O) groups.

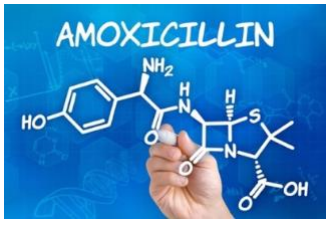

Fig.7 Amoxicillin available since 1972 also has three carbonyl (C=O) groups.

Since plasma levels of amoxicillin are 2–3 times higher than for ampicillin, it is likely to be more diabetogenic than ampicillin, unless the dose has been adjusted to allow for this increase. The dose of ampicillin in the BNF March – September 2023 for a child 5–11yrs is 500mg x4pd, whereas the dose for amoxicillin for a child of the same age is 500mg x3pd. Therefore, the total daily dose for ampicillin is 2,000mg and 1,500mg for amoxicillin, which doesn't take into account the difference in plasma levels.

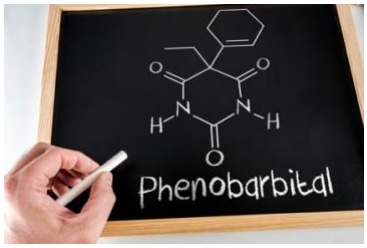

Fig.8 Phenobarbital used for insomnia and seizures has structural similarity to the diabetogenic drug alloxan.

In my studies of diabetic children in England, I had one child who was diagnosed at 4yrs who had only been exposed to phenobarbital in-utero and had been exposed to only one other drug ampicillin, taken 11 days prior to the diagnosis of T1D. It's easy to accept that phenobarbital can be diabetogenic due to its chemical structural similarity to alloxan. In support of this, it has been shown that two different chemical modifications of alloxan, by the addition of a side group to the ring structure, also produced diabetes in rodents[15].

Now for caesareans. A meta-analysis of 20 studies worldwide reported in 2008[16] that caesareans are linked to T1D in children. The drug oxytocin is routinely used for caesareans to promote uterine contraction and is also used for inductions. In my study that captured all 36 diabetic children diagnosed by the age of 12yrs, 40% of them had been induced. Oxytocin has 11 carbonyl groups.

When I asked for clarification from The Royal College of Obstetricians and Gynaecologists in London as to whether oxytocin is given during or after a caesarean, they would not answer the question. I had informed them that there are many reports linking caesareans to the onset of T1D.

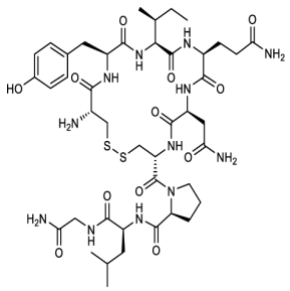

Fig.9 Oxytocin is used in inductions and has eleven carbonyl groups.

Therefore, any study looking for a link between antibiotics and diabetes also needs to ask whether any drugs were administered during labour. If oxytocin was given, the dose also needs to be recorded as this will vary

according to how long labour takes. Since antibiotics are given before a caesarean to try to prevent an infection, this also needs to be documented.

Therefore any study of the aetiology of diabetes needs to collect data about all drugs that the child was exposed to in-utero and during labour, as well as the dose, drugs taken after birth until diagnosis of diabetes and the quantity and type of food and drink taken by the child for about 2 hours before and after taking antibiotics. This is impossible for any retrospective study and too demanding for any prospective study, as one would have to calculate the concentration of trace minerals and sugars in the food and drink consumed, for reasons explained above.

Studies that report a link between antibiotics and T1D as shown in table 1 are few and there are many that state that there is no link[17]. If the studies recorded antibiotics taken by the mother during pregnancy[18,16] they didn't make a note of any other drugs taken during pregnancy or any herbal remedies. And no study has to my knowledge asked whether the child was induced.

Year	Country	Conclusion
2006	Finland	Use of Pen-V or quinolone before pregnancy associated with increased risk of diabetes in child. Risk higher where macrolides used both by mother before pregnancy and by the child[19].
2015	UK	Treatment with 2-5 antibiotic courses associated with increase in diabetic risk for penicillin, cephalosporins, macrolides and quinolones[20].
2016	Denmark	Redemption of broad-spectrum antibiotics during infancy is associated with an increased risk of childhood T1D in children delivered by caesarean section[21].
2020	Sweden	Antibiotics in the first year of life is associated with increased risk of T1D before 10yrs most prominently in children delivered by caesarean section[22].

Table 1. Publications that report a link between antibiotics and T1D.
Pen-V has three carbonyl groups, macrolides can also have three and quinolones have two.

Table 2. shows some publications that report a link between antibiotics and T2D in adults.

Year	Country	Conclusion
2015	Denmark	Results support possibility that antibiotic exposure increases T2D risk[23].
2019	USA	Any and repeated exposure to certain antibiotics may increase diabetes risk[24].
2020	USA	Longer duration of antibiotic use associated with risk of T2D in women[25].
2021	Korea	People who used antibiotics for 90days had higher risk of diabetes[26].
2022	Finland	Each antibiotic course during young adulthood was associated with 2-4% increase in risk of developing T2D[27].

Table 2. Publications that have reported a link between antibiotics and T2D.

Statins like antibiotics, have also been linked to diabetes, this time T2D[28,29]. Atorvastatin (Lipitor) which was the most frequently prescribed drug in England, the USA and Australia around 2022 has two carbonyl groups. Some patients can progress from T2D to T1D, and I consider T2D to be a case of there being a sufficient number of functioning beta-cells for the patient not to require insulin. As shown below, there was a duration and dose-dependent effect so with continued use the patient may eventually require insulin. Diet and weight are factors that will affect the time taken to progress from T2D to T1D.

T2D which used to be called maturity onset diabetes (MOD) occurring mainly after forty years of age, is now accepted as existing in children and has been increasing over the decades. I consider this increase to be due to doctors being more aware of diabetes in children and therefore testing blood sugar levels.

Year	Country	Conclusion
2013	Canada	Treatment with Lipitor and Zocor might be associated with an increased risk of diabetes[30].
2013	Ireland	Statin use associated with increased risk of diabetes with a significant duration and dose effect[31].
2015	Scotland	Patients on statin treatment had a 46% increased risk of T2D. Dose dependent for Lipitor and Zocor[32].
2017	Australia	Statin use associated with higher risk of diabetes. Risk increased with increasing dose[33].
2017	USA	Statin use associated with greater diabetes risk[34].
2020	Korea	Statin use was significantly associated with an increased risk of new-onset type 2 diabetes. We also found a dose-response relationship in terms of statin use duration and dose[35].

Table 3. Some publications that report a link between statin use and T2D.

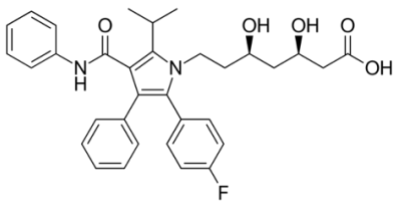

Fig.10 Chemical structure of atorvastatin which has two carbonyl (C=O) groups.

Seven of the nine statins currently available have two carbonyl groups and two have a carbonyl (C=O) and a sulphonyl group which also has negatively charged oxygen ions.

To conclude, insulin dependent diabetes is currently considered to be an auto-immune disease and changes in the gut microbiome consisting of microorganisms that include bacteria, fungi and viruses have been *hypothesized* as causing diabetes, as a result of disruption to the microbiome which impacts the immune system[36] thereby causing diabetes.

I find this argument to be flawed because the microbiome is affected by infections and diet[37], so any study which puts the blame on the microbiome for a disease, would need information about what was eaten and what medications were taken by subjects in the study, since both affect the composition of the microbiome.

Additionally, any faecal studies to identify and quantify bacteria in the gut are unlikely to give accurate results, as only a fraction of the sample is examined and would not be representative of the 100 trillion bacterial cells[38] reported to be in the gut. As for cells of the immune system being affected by a change in the microbiota, beta-lactam antibiotics are known to interfere with T cell metabolism[39] so any studies would need to know what drugs had been taken and when. Preservatives which are ubiquitous in food these days are also known to affect the microbiota.

It is my view therefore, that ruptured beta-cells of the pancreas which can arise from ingestion of drugs which contain negatively charged oxygens, are seen as foreign to the body. And that this causes the immune system to produce autoantibodies directed against the beta-cells. These autoantibodies form in *response* to the formation of ruptured beta-cells.

Diabetogenic chemicals destroy the insulin producing capability of the beta-cells of the pancreas in a dose-dependent way, as shown in animals and as is evident from information in tables 2 and 3. So it is only when one has been exposed to enough of a diabetogenic drug that symptoms of insulin dependent diabetes become apparent.

As a result of the facts described above, I believe that both insulin and non-insulin dependent diabetes are iatrogenic diseases. Iatrogenesis resulting from exposure to a variety of drugs, in particular antibiotics as they are amongst the most frequently prescribed in the UK. I am also of the opinion that other diseases that are classed as autoimmune are in fact iatrogenic.

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